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# Evaluation of electrocardiographic arrhythmogenicity markers in patients with type 2 diabetes mellitus

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## ABSTRACT

**Aims**: Diabetes mellitus (DM) is a chronic disease that progresses with hyperglycemia and the proinflammatory process. The most common complication of DM is cardiovascular disease, and it is known that the risk of arrhythmia increases in patients with DM. The aim of our study was to evaluate the correlation of electrocardiographic arrhythmogenicity markers with HbA1c and fasting blood glucose.

**Methods**: The study included 77 type 2 DM patients and 76 healthy individuals as a control group. Body mass index, HbA1c value, and fasting blood glucose level were recorded for all patients. Corrected QT (QTc), T peak-T end intervals (Tp-e), and Tp-e/QTc values were calculated from 12-lead electrocardiography (ECG). The results were evaluated statistically.

**Results**: The Tp-e interval ($p<0.001$), QTc interval ($p<0.05$), and Tp-e/QTc ratio ($p<0.001$) were significantly prolonged within the DM group compared to the control group.

**Conclusion**: ECG, an inexpensive and reliable diagnostic method, can be used to evaluate the risk of arrhythmia in DM patients. This study concluded that QTc, Tp-e interval, and Tp-e/QTc ratio are markers that can be used to predict arrhythmia risk in DM patients.

**Keywords**: Arrhythmia, diabetes mellitus, HbA1c, QTc, T peak-T end interval, Tp-e/QTc

## INTRODUCTION

Type 2 diabetes mellitus (DM) is a complex metabolic disease that progresses with beta cell destruction and insulin resistance, resulting in hyperglycemia.[1] The most common cause of morbidity and mortality in DM is cardiovascular disease. Prospective studies show that the risk of coronary artery disease and myocardial infarction in patients with DM increases 1-3 times in men and 2-5 times in women compared to healthy individuals.[2] Another cardiac complication seen in patients with DM is ventricular arrhythmia. Cardiac autonomic neuropathy is seen in approximately 30% of patients with DM.[3] Impaired autonomic regulation in patients with DM causes increased activation of the sympathetic system and is associated with ventricular arrhythmia independent of coronary artery disease, heart failure, and hypertension.[4] In addition to autonomic neuropathy, the prothrombotic and proinflammatory process seen in patients with DM also contributes to the development of atherosclerosis, increasing the risk of silent infarcts and arrhythmia.[5] Many studies have shown that an electrocardiogram (ECG) can be used to predict the risk of cardiac arrhythmia in patients with DM. QTc is one of the most commonly used predictors in these studies.[6,7] QTc prolongation has been shown to be an independent predictor of cardiovascular mortality in patients with DM.[8] Two other recently studied markers, the T peak-T end interval (Tp-e) and the Tp-e/QT ratio, are also increasingly used.[9,10] Tp-e has been reported in previous studies to be able to show transmural repolarization. Tp-e is measured independently from the QRS complex, and the Tp-e interval measurement is considered superior to that of QTc duration.[11]

The aim of this study was to determine the relationship between QTc, Tp-e, and the Tp-e/QTc ratio, which are among the arrhythmogenicity indices, and blood glucose regulation in patients with DM.

## METHODS

The study was carried out with the permission of Kahramanmaraş Sütçü İmam University Clinical Researches Ethics Committee (Date: 01.12.2021, Decision No: 01). This study was conducted in our institution between January and June 2022. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Patients with type 2 DM who applied to an endocrinology and metabolic diseases outpatient clinic for a routine check were included in this cross-sectional study. The patients included in the study were between the ages of 18-65. Blood pressure measurements were taken during the physical examination, and patients who were normotensive without medication or under medication were included in the study. The exclusion criteria were as follows: 1) patients using beta-blockers, calcium channel blockers, or antiarrhythmic drugs; 2) patients with renal dysfunction or electrolyte imbalance; 3) patients with any history of arrhythmia, known coronary artery disease, heart valve disease, pacemaker implantation, or cardiomyopathy; 4) patients with thyroid dysfunction; 5) patients with clinical and/or laboratory findings suggestive of infection; 6) patients using cigarettes, alcohol, and recreational drugs; 7) patients with a diagnosis of malignancy; and 8) pregnant patients.

For the control group, healthy individuals who did not have a history of chronic disease, met the inclusion and exclusion criteria, applied to our hospital for a check-up, and were age- and gender-matched with the patient group were included.

Venous blood samples were taken in the morning after 12 hours of fasting. Biochemical analyses of fasting blood glucose and hemoglobin A1c (HbA1c) were performed. Weight and height measurements were taken, and body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2).

The 12-lead ECGs of the individuals under study were evaluated. A resting ECG was recorded at 50 mm/sec paper speed (Nihon Kohden ECG-1250 electrocardiograph). The Tp-e interval was defined by the tangential method. The QT interval was descriptive of the time from the onset of the QRS complex to the point where the T wave reversed from baseline. The QTc interval was computed by the Bazett's formula.[12] Precordial V5 lead was applied to these measurements. The evaluation of ECGs in the study was performed by an endocrinologist who had training in cardiology and had previous studies on ECG.

### Statistical Analysis

We conducted all analyses utilizing R software, version 4.0.4, developed by the R Foundation for Statistical Computing in Vienna, Austria. Continuous variables were presented as mean±standard deviation, or as median (interquartile range), while categorical variables were expressed as counts (n) and proportions (%). To compare continuous variables between groups, either the Student t-test or the Mann-Whitney U test was employed, based on the normality distribution of the data. Categorical variables were assessed for group differences using the Chi-square test. For numerical variables with a homogeneous distribution, correlation coefficients were calculated using the Pearson test, and for those with a non-homogeneous distribution, the Spearman test was utilized. Statistical significance was considered for two-tailed p-values less than 0.05.

## RESULTS

Table 1 shows the baseline clinical and laboratory characteristics of both the patients with DM and control groups. A total of 153 patients were included in the study, including 88 women (57.5%) with a mean age of 43±13.2 years and 65 men (42.5%) with a mean age of 44.5±11.2 years. Among them, the control group consisted of 76 patients while the DM group consisted of 77 patients. Notably, no significant differences were observed between the groups in terms of gender, age, or BMI.

As expected, the DM group had increased fasting glucose and HbA1c levels compared to the control group ($p<0.05$). In addition, the Tp-e interval ($p<0.001$), the QTc interval ($p<0.05$), and the Tp-e/QTc ratio were significantly prolonged within the DM group compared to the control group.

When performing a correlation analysis within the DM patient cohort, Tp-e intervals were found to have significant positive correlations with duration of DM ($r=0.423$, $p<0.001$), BMI ($r=0.339$, $p=0.003$), and

**Table 1.** Comparing basic characteristics and laboratory data between groups

| | Total (n=153) | Controls (n=76) | Cases (n=77) | p |
|---|---|---|---|---|
| Sex (female), n(%) | 88(57.5) | 46(60.5) | 42(54.5) | 0.514 |
| Age (years) | 46.2 ± 11.7 | 44.1 ± 9.7 | 48.3 ± 13.6 | 0.065 |
| BMI kg/m² | 27(24-29) | 27.1(24.3-29) | 27(24-29) | 0.427 |
| DM Duration (years) | ------- | ------- | 8(5-11) | ------- |
| Fasting glucose, mg/dl | 102(88-135) | 92(78-102) | 130(100-194) | <0.001 |
| HbA1c, mg/dl | 6.3(5.7-8.3) | 5.7(5.5-6) | 8(7.2-10) | <0.001 |
| QTc (ms) | 415(409-423) | 413(409-420) | 418(410-425) | 0.039 |
| Tpeak-tend (ms) | 84(76-89) | 78(73-84) | 88(82-95) | <0.001 |
| Tpeak-tend/QTc | 0.20(0.18-0.21) | 0.18(0.17-0.20) | 0.21(0.19-0.22) | <0.001 |

BMI: Body Mass Index, DM: Diabetes Mellitus, QTc: corrected QT p < .05, ** p < .01, *** p < .001

HbA1c values (r=0.463, p<0.001) as shown in **Figure 1**. Likewise, the QTc interval showed significant positive correlations with BMI (r=0.367, p=0.001) and HbA1c (r=0.306, p=0.007), while no correlation was found between QTc and the duration of DM (r=0.171, p=0.136). The Tp-e/QTc ratio was positively correlated with DM duration (r=0.370, p=0.001) and HbA1c levels (r=0.369, p=0.001), while there was no significant correlation between Tp-e/QTc ratio and BMI ( r=0.220, p=0.055) (**Table 2**).

## DISCUSSION

The sudden cardiac death rate for patients with DM is 2-10 times higher than for the general population, but the underlying causes are still unclear.[13] Arrhythmias are thought to be the most important cause of sudden cardiac death, and QTc prolongation is one of the most important arrhythmia markers for DM patients.[14] Similar to previous studies, our study found a significant prolongation of QTc between the DM and control groups.[9,10,14] A study by Stern et al.[15] on 265 patients showed that besides the presence of DM, the patients' blood sugar regulation and BMI values were directly related to QTc prolongation. The authors determined that high HbA1c and obesity cause cardiac autonomic dysfunction, resulting in an increased risk of arrhythmia. Similarly, we observed that both HbA1c levels and BMI were positively correlated with QTc. Many studies have shown that a high fasting blood glucose level is a risk factor for QTc prolongation in patients with DM.[14-16] However, our study revealed no significant relationship between QTc and fasting blood glucose. This may be due to the limited number of patients in our study, but it may also be because the blood glucose regulation of the patients included in the study was relatively well controlled. As a result, the fasting blood glucose levels of our patients were close to normal. In the literature, we could not find any study evaluating the relationship between DM duration and QTc interval; however, Agarwal et al.[17] showed that the duration of DM increases the risk of atrial fibrillation. In our study, we found no significant relationship between DM duration and QTc interval, but there was a significant positive correlation between DM duration and both Tp-e and the Tp-e/QTc ratio.

Tp-e and the Tp-e/QTc ratio are two of the ventricular arrhythmia markers frequently studied in the last decade, and in some clinical conditions, these markers have been shown to be more useful for predicting cardiac arrhythmias than QTc.[18] Similarly, our comparison of the DM and control groups

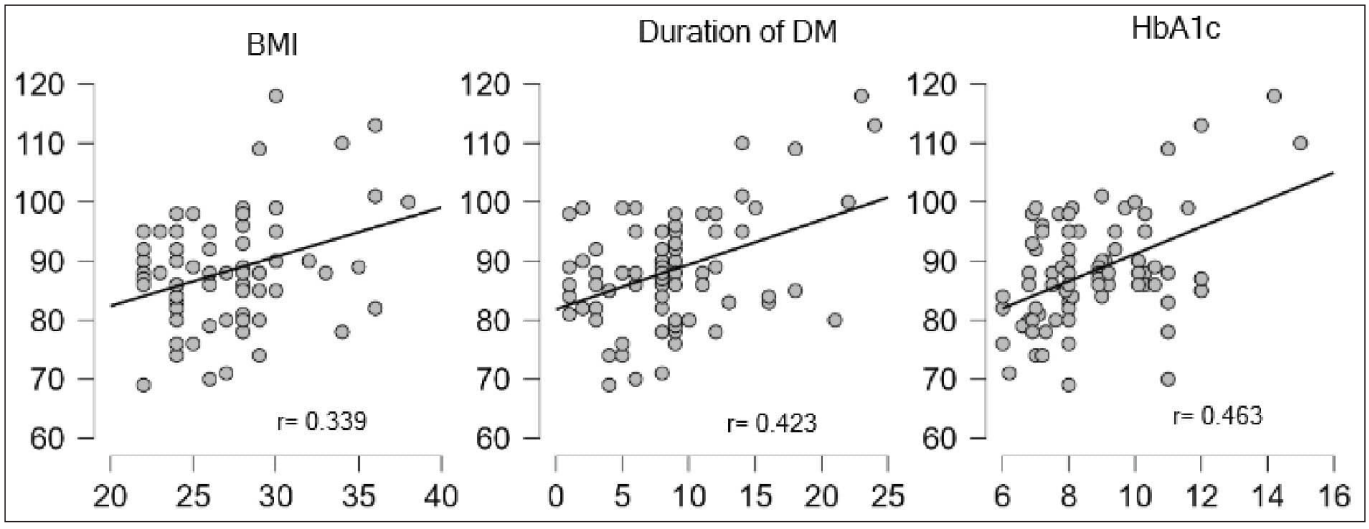


**Figure 1.** Positive Correlation Between Body Mass Index (BMI), Duration of Diabetes Mellitus (Years) and HbA1c Values With The Tpeak Tend Interval (Tp-e).

**Table 2.** Correlation matrix between variables

| Variable | | QTC | Tpe | Tpe/QTc | Duration of DM | HbA1c | BKI | Glucose |
|---|---|---|---|---|---|---|---|---|
| Duration of DM | r-value | 0.171 | 0.423*** | 0.370*** | — | | | |
| | p-value | 0.136 | <.001 | <.001 | — | | | |
| HbA1c | r-value | 0.306** | 0.463*** | 0.369*** | 0.311** | — | | |
| | p-value | 0.007 | <.001 | <.001 | 0.006 | — | | |
| BMI | r-value | 0.367** | 0.339** | 0.220 | 0.327** | 0.215 | — | |
| | p-value | 0.001 | 0.003 | 0.055 | 0.004 | 0.061 | — | |
| Fasting glucose | r-value | 0.033 | -0.155 | -0.160 | -0.048 | 0.087 | 0.057 | — |
| | p-value | 0.776 | 0.179 | 0.166 | 0.682 | 0.454 | 0.622 | — |

BMI: Body Mass Index, DM: Diabetes Mellitus * p < .05, ** p < .01, *** p < .001

showed that Tp-e and Tp-e/QTc gave more significant results than QTc. In previous studies, it was observed that Tp-e and Tp-e/QTc are directly related to HbA1c and fasting blood glucose levels in patients with DM.[9,10] Similar results were seen in the study by Ardahanlı et al.[19] on prediabetic patients, in which it was theorized that silent ischemic heart diseases may occur in the prediabetic period, so the risk of ventricular arrhythmia increases with an increased transmural dispersion of repolarization. Similarly, we found a positive correlation between HbA1c and Tp-e and Tp-e/QTc. However, unlike previous studies, we found no relationship between fasting blood glucose and arrhythmogenicity indices, which again may be due to the relatively regulated blood glucose levels of the DM group included in our study.

Conflicting results have been seen in studies evaluating the relationship between the duration of DM and cardiac complications. While some studies have shown that the risk of subclinical and clinical cardiovascular disease increases with longer durations of DM,[20,21] some studies have not found any association.[22] In our study, Tp-e and Tp-e/QTc were found to be directly related to the duration of DM, independent of blood glucose regulation.

Previous studies have shown that obesity increases the risk of arrhythmia, and that both Tp-e and Tp-e/QTc increase in obese patients.[23,24] There is a pathophysiology of increased risk of arrhythmia with obesity; especially in the early stages of obesity, there is thought to be a decrease in cardiac remodeling and an increase in fibrosis.[25] In addition, cardiometabolic risk due to increased sympathetic activity increases in obesity.[26] Similarly, we found a positive correlation between Tp-e and BMI.

### Study Limitations

This research had some limitations. First, the sample size was relatively small, so there is a need to conduct this study in a larger population. Second, it used a cross-sectional research method and had no long-term patient follow-up. Also not including diabetic patients with arrhythmia as a third group in the study is a factor that reduces the power of the study. Finally, some of the patients included in the study had chronic diseases, such as hypertension and hyperlipidemia, apart from DM. We included normotensive patients in the study, but we had to disregard the effect of chronic diseases other than DM on the arrhythmia markers. Therefore, further studies with more isolated and larger patient groups are needed to reveal the pathophysiology of arrhythmia in patients with DM.

## CONCLUSION

The most common cause of mortality due to DM is cardiovascular complications. One of these complications is arrhythmia. Because it is an inexpensive and reliable diagnostic method, ECG should be used in the evaluation of cardiac complications in DM patients. As a result of our study, QTc, Tp-e interval and Tp-e/QTc ratio are markers that can be used to predict arrhythmia risk in patients with DM.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Kahramanmaraş Sütçü İmam University Clinical Researches Ethics Committee (Date: 01.12.2021, Decision No: 01)

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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